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# PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Barnes & Thornburg
11 South Meridian Street
Indianapolis, IN 46204
ETATS-UNIS D'AMERIQUE

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 06.09.2005 |
| Applicant's or agent's file reference<br>3220-75156 | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2004/014097 | 06.05.2004 | 06.05.2003 |

Applicant
PURDUE RESEARCH FOUNDATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>3220-75156 | **FOR FURTHER ACTION** See Form PCT/IPEA/416 | |
| International application No.<br>PCT/US2004/014097 | International filing date *(day/month/year)*<br>06.05.2004 | Priority date *(day/month/year)*<br>06.05.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K47/48, A61P37/00, A61K51/04 | | |
| Applicant<br>PURDUE RESEARCH FOUNDATION | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| | |
|---|---|
| Date of submission of the demand<br>04.03.2005 | Date of completion of this report<br>06.09.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office - P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040 Tx: 31 651 epo nl<br>Fax: +31 70 340 - 3016 | Authorized Officer<br>Dullaart, A<br>Telephone No. +31 70 340-3290 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/014097

10/552569

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-17 as originally filed

**Claims, Numbers**

1-6 filed with telefax on 04.03.2005

**Drawings, Sheets**

1/3-3/3 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/014097

## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-5 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/014097

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-6 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-6 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-6 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III.**

In the present application, the International Searching Authority has restricted the search because of the following objections under Articles 5 and 6 PCT.
Originally filed claims 1-8 related to the use of an extremely large number of possible conjugates. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the conjugates claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the conjugates used in the examples.
In response to this objection from the International Searching Authority, the applicant has amended the claims, limiting the scope to what has been searched.

**Re Item IV.**

The International Searching Authority has raised an objection for lack of unity of invention in the application as originally filed.
In reaction to this objection, raised by the International Searching Authority, the applicant has limited the scope of protection sought to the first subject.

**Re Item V.**

1 The following documents are referred to in this communication:

**D1: WO 02/087424 A (TURK MARY JO ; LOW PHILIP STEWART (US)) 7 November 2002 (2002-11-07)**

**D2: WO 99/41285 A (MEDAREX INC) 19 August 1999 (1999-08-19)**

**D3: WO 96/36367 A (PURDUE RESEARCH FOUNDATION) 21 November 1996 (1996-11-21)**

**D4: Reddy J A et al: "Folate-mediated targeting of therapeutic and imaging agents to cancers"**
**Critical Reviews in Therapeutic Drug Carrier Systems, vol. 15, no. 6, 1998, pages 587-627, XP000901554 ISSN: 0743-4863**

**D5: WO 01/74382 A (PURDUE RESEARCH FOUNDATION) 11 October 2001 (2001-10-11)**

**D6: Nakashima-Matsushita N et al: "Selective expression of folate receptor β and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis"
Arthritis and Rheumatism, Lippincott, Philadelphia, US, vol. 42, no. 8, August 1999 (1999-08), pages 1609-1616, XP002284073 ISSN: 0004-3591**

**D7: Turk M J et al: "Folate-targeted imaging of activated macrophages in rats with adjuvant-induced arthritis"
Arthritis and Rheumatism, Lippincott, Philadelphia, US, vol. 46, no. 7, July 2002 (2002-07), pages 1947-1955, XP004536129 ISSN: 0004-3591**

**D8: WO 98/58678 A (DEN HARTOG MARCEL THEODORUS ; BOER MARK DE (NL); PANGENETICS B V (NL)) 30 December 1998 (1998-12-30)**

Document **D1** discloses the treatment of diseases mediated by macrophages. Page 1 specifically mentions SLE as disease to be treated. The procedure followed in examples 1-8 closely resembles the one followed in the present application. Also, EC20 (see present example 1) is accumulated specifically in inflamed tissue: see example 11 and figure 4.
In view of this document, which contains all the features of the present inventions, these inventions do not meet the requirements of Article 33.2 PCT for novelty.
The applicant has argued, that the present application is directed to a so-called "selection invention". In order to fulfil the criteria for a selection invention, the selection should be purposive, i.e., it should lead to a specific, different effect. The obtained effect (the problem to be solved) is the treatment of lupus erythematosus.
Though lupus erythematosus has been mentioned in the introductory paragraph of D1, which exactly the same wording as the introduction of the present application, D1 does not disclose the treatment of lupus erythematosus. Therefore the International Preliminary Examination Authority considers, that the presently claimed use fulfills the requirements of Article 33.2 PCT for novelty.

With regard to the use of certain specific conjugates to fulfil the requirements of novelty, **D1** is still considered to be the closest prior art. The use of the specific conjugate is a further distinguishing feature. The problem to be solved is the treatment of lupus erythematosus.

Document **D3** discloses the conjugates of folic acid presently claimed.
Document **D4** discloses folate-mediated targeting of therapeutic agents to cancers.
Document **D5** discloses the same process of immunisation against FITC, followed by administration of a conjugate folate-FITC. This elicits an immune response to the targeted cells. Example 1 describes the effect of folate-fluorescein isothiocyanate conjugates on survival of mice with lung tumour implants; examples 4 and 6 on tumour growth.
Document **D6** discloses the selective expression of folate receptor β and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis
Document **D7** discloses folate-targeted imaging of activated macrophages in rats with adjuvant-induced arthritis, using the compound also used in present example 1.

In principle, the skilled person would not need his inventive skills to exchange one conjugate for another. Therefore, in order to be more than merely replacing one conjugate by another, an intended effect should be demonstrated. This intended effect is indeed demonstrated in example 2 of the present application, showing the actual treatment of lupus-prone mice by the conjugate FITC-folate. Therefore the International Preliminary Examination Authority considers the present application to meet the requirements of Article 33.3 PCT for inventive step.

**Re Item VIII.**

Independent claim 1, as well as dependent claims 2-5, encompass a genus of compounds, in which the groups L and X are defined only by their function: "a folate-receptor binding ligand" or "folate or an analog thereof" (emphasis added) for L, and "an immunogen" for X, wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognised based upon information readily available to one skilled in the art, the person skilled in the art would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that are particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Since claims 1-5 only

provide a partial further definition of the compound, they do not fulfil the requirements of Articles 5 and 6 PCT.

CLAIMS:

1. Use of a conjugate of the general formula

L-X

where the group L comprises a ligand capable of binding to activated macrophages and the group X comprises an immunogen, where the group L comprises a folate receptor binding ligand, in the manufacture of a medicament for treating lupus erythematosus.

2. Use of claim 1 where the group L comprises folate or an analog thereof.

3. Use of claim 1 where the group L comprises folate.

4. Use of claim 1 where the immunogen comprises fluorescein isothiocyante or dinitrophenyl.

5. Use of claim 2 where the immunogen comprises fluorescein isothiocyante or dinitrophenyl.

6. Use of claim 3 where the immunogen comprises fluorescein isothiocyante or dinitrophenyl.